Docket No.: 616292000111
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of: David C. BAULCOMBE et al.	Confirmation No.: 9959
Application No.: 10/805,804	Art Unit: 1638
Filed: March 22, 2004	Examiner: Ashwin D. Mehta, Ph.D.
For: GENE SILENCING	

REPLY BRIEF TO EXAMINER'S ANSWER

MS Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

An Examiner's Answer (EA) to the Appellants' Appeal Brief was mailed 26 June 2009, setting a date of 26 August 2009 for filing this Reply Brief.

It is assumed that this Brief will be read in combination with the original Appeal Brief, and therefore, only arguments in response to the EA are presented herein, with all other arguments from the Appeal Brief being incorporated by reference. Although not required, a listing of the claims is attached for the Board's convenience.

5. Summary of Claimed Subject Matter

It is stated in the EA that the summary of the claimed subject matter contained in the Brief is deficient because it states that the short RNA molecules (SRMs) have any number of nucleotides between 20 and 30 including 20-24. It is asserted that: "While the specification teaches that the SRMs are 20-30 nucleotides in size, the size of the SRMs used in the method of the appealed claims is limited to consisting of 20, 21, 22, 23, 24 nucleotides." This has no bearing on the current appeal. The Examiner has never objected to the limitation to the 20-24 size range and this is fully supported by the specification at page 4, lines 4-14.

Appellants have indeed elected the species of plants, for purposes of examination, not as a separate invention. If the claims are found patentable with respect to plants, examination as to other species encompassed by the generic claims is required.

As the EA mentions, the original Summary of the Invention further specified what the inventors considered their inventive concept – namely that it is short (20-24 nucleotide) RNA molecules, *i.e.*, short sense RNA molecules (SSRMs) and short antisense RNA molecules (SARMs) that are the immediate effectors of gene silencing – representing an advance over the prior art knowledge that double-stranded RNA of longer lengths was successful in silencing genes in nematodes. By virtue of this discovery, preparation of compositions for gene silencing is made much more practical. It is important to recognize that it is the length of the SSRMs and SARMs that constitutes the invention; there is no assertion that the role of sense and antisense strands of RNA in gene silencing was previously unknown. What must be found in the cited documents is a teaching of short RNA molecules of this specific size.

9. Grounds of Rejection and 10. Response to Arguments

Graham

Claims 125-130 continue to be rejected as anticipated under 35 U.S.C. § 102(e) as being anticipated by Graham (US Patent No. 6,573,099). The issue here is what Graham does or does not disclose. In the EA, the Examiner continues to dispute the following positions of Appellants:

1. Graham never discusses size of RNA produced, only the size of "structural genes", and transcription typically adds more nucleotides – the Examiner's reliance on the inclusion of the T7 promoter among promoters listed in Graham is inconsistent with legal precedent and it is wrong scientifically;
2. Graham teaches a minimum of 30 nucleotides is required even for the structural gene; and
3. Graham teaches a large range of sizes for the structural gene and does not anticipate lengths of 20-24 nucleotides even for the structural gene, much less the RNA it generates.

If any one of these positions is correct, Graham does not anticipate.

1. Graham never discusses anywhere the length of any RNAs that are produced by Graham's constructs. The Examiner has never pointed to any explicit disclosure in Graham as to the length of RNAs that are produced, because none exists. The Examiner's position is based on inherency, and ignores the legal requirements for inherent anticipation.

For inherency to be found, the claim limitation must be an inevitable and unfailing result of what is taught. In addition to *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F2d 1264, 20 USPQ2d 1746 (Fed. Cir. 1991) cited in the Appeal Brief, also relevant is the well known case involving Zantac®, *Glaxo, Inc. v. Novopharm, Ltd.*, 52 F3d 1043, 34 USPQ2d 1565 (Fed. Cir. 1995)

cert. denied 516 U.S. 988 (1995). As the Board will recall, an example in an earlier patent for preparing an older form of the drug, which example once in a while produced the claimed new form of Zantac®, but not always, was held not to anticipate.

The Examiner's case for inherent anticipation completely rests on Graham's inclusion of the T7 promoter among a multitude of other promoters, which other promoters, all agree, do extend the length of the RNA produced beyond the limits of the gene transcribed. The Examiner asserts that because the T7 promoter does not add a polyA tail, the present claims are anticipated. Since not only the T7 promoter is contemplated, but a multitude of others that clearly result in extended RNA molecules, according to *Glaxo*, Graham, taken as a whole, does not anticipate. Even if only the T7 promoter portion of Graham is focused on (which is improper), the Examiner's position is unsupportable because to the best of the undersigned's knowledge, there are only three ways T7 can terminate transcription:

A. By "run off": this is done ***in vitro*** and essentially involves the T7 RNA polymerase falling off the end of its DNA template and hence transcription terminates. This can only be done if one can cleave the DNA template strand. This is easy to do *in vitro* (e.g with restriction enzyme action) but cannot be done *in vivo*, as far as is known to the undersigned, and it is certainly not disclosed in Graham how to achieve this, and it is even not clear how this could be achieved today;

B. By using a hairpin terminator: in this situation the T7 RNA polymerase disengages from it's DNA template **after** it has transcribed an inverted repeat DNA sequence inserted at the back end of each strand of the structural gene. This would therefore not produce SSRM and/or SARM having the size of the structural gene;

C. By using a fragment of the Pth gene: in this situation transcription termination of T7 occurs only **after** sequence within the Pth fragment has been transcribed and included in the

transcript, so that, even if not poly-adenylated, the sequence would be longer than that of the structural gene.

In addition, for the T7 promoter to operate in plants, it would also have been necessary to provide the plants with an expression system for producing the T7 RNA polymerase (which is encoded by a gene from the T7 bacteriophage and is not present in plants or other eukaryotes such as mammals). This is neither disclosed nor suggested in Graham. Appellant would be pleased to provide evidence in support of the facts stated in A-C above concerning T7 polymerase, but this does not seem to be permitted at this stage of the proceedings. Such evidence would have been submitted previously had the Examiner previously relied on Graham's mention of the T7 polymerase as a basis for asserting that Graham teaches production of short RNA molecules *in vivo*. This argument appears for the first time in the EA. If the Examiner wishes this interpretation of Graham to be considered on appeal, and questions Appellants' statements of fact, it should be required of the Examiner to present evidence to the contrary.

It seems quite a stretch, based on the inclusion of T7 promoters in a laundry list of promoters in Graham, to assert that Graham inherently anticipates production of any RNA with exactly the same number of nucleotides that is present in Graham's structural gene, particularly where there is also no teaching in Graham to suggest that this would even be a desirable goal to achieve.

Clearly, the holding in *Net MoneyIn, Inc.* cited in the Appeal Brief is apposite – a number associated with substance A (the structural gene) cannot be automatically assigned to a different substance B (the RNA produced).

2. It is not correct that Graham teaches even a structural gene having 20-30 nucleotides similar to or identical to a region of the target gene. According to the EA, column 6, lines 25-27 of

Graham, demonstrates that the structural gene component comprises at least about 20-30 nucleotides in length specifically derived from a viral DNA polymerase and several additional named end products. This is inconsistent with the clear statement in column 5 that there is a "requirement" that the synthetic gene is "substantially identical" at the nucleotide sequence level to at least 30 or more contiguous nucleotides of the target gene.

There is an explanation for this apparent inconsistency and it does not involve a result wherein 20-30 nucleotides is the total length of the structural gene. In the discussion in column 5, at line 21, Graham states that

> A gene of the invention may be subjected to mutagenesis to produce single or multiple nucleotide substitutions, deletions, and/or additions without affecting its ability to modify gene expression. Nucleotide insertional derivatives of the synthetic gene of the present invention include 5′ and 3′ terminal fusions as well as intrasequence insertions of single or multiple nucleotides.

The language in column 6, line 25-27, "the structural gene components of the synthetic gene comprise at least about 20-30 nucleotides in length 'derived' from a viral DNA polymerase, etc" is consistent with the minimum requirement of 30 nucleotides in the structural gene if it is assumed to require that only 20 nucleotides from the target gene need be found in the structural gene anywhere and various insertions may occur to extend the length, to at least 30 nucleotides, while still maintaining substantial identity.

The EA also notes, at page 13, that claims 11 and 12 of Graham are evidence that Graham describes structural gene sequences of 20 to 30 nucleotides in length. However, this is not what the claims say. Claims 11 and 12 refer not to the structural gene but rather to the "region of the target gene", consistent with the "derived from" language in column 6. The structural gene in claim 2, for example, is described as a "structural gene sequence comprising a nucleotide sequence that is

substantially identical to at least a region of said target gene." This says nothing about the size of the structural gene itself; it only must have nucleotides in it that are substantially identical to a gene region that contains 20-30 nucleotides according to claim 11 of Graham. In view of the discussion in column 5, beginning at line 21, regarding insertions, etc., is it clear that this does not limit the size of the structural gene itself, much less any RNA produced.

It may also be telling that it was not until late in prosecution, subsequent to the publication in October, 1999 of the present inventors' paper in *Science* (of record), that the claims in the Graham application were amended to include claims 11 and 12, as noted by reviewing the Graham patent prosecution history on Public PAIR.

3. At page 13 to 14, the EA in discussing *Atofina v. Great Lakes Chem. Corp.*, asserts Graham describes a genus of structural gene lengths of 20-30 nucleotides. But Graham does not disclose this genus – Graham only says that 20-30 nucleotides in the structural gene must be *derived* from specific target genes (column 6, lines 25, *et seq.*). This is not a description of the length of the structural gene itself, much less of the RNA produced. Thus, the citation of *Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.* and *In re Petering* that the "disclosure of a small genus may anticipate the species of that genus even if the species are not themselves recited" is inapposite. The "genus" of structural gene lengths described by Graham is, at a minimum, the 20-1,385 nucleotides genus recited the Appellants' Brief even if the possibility of *structural gene* lengths as low as 20 is accepted (which it is not). Properly read, the Graham "genus" of structural gene lengths is 30-1,385 nucleotides, which may contain 20-30 nucleotides derived from particular target genes. Graham, by teaching constructs in the range of 30 to 1,385 nucleotides, or even 20 to 1,385 nucleotides, cannot

anticipate or even suggest the claimed range of 20-24 nucleotides even of a structural gene, let alone the particular species of RNA claimed having 20, 21, 22, 23 and 24 nucleotides.

Page 14 of the EA, states that "It is unclear how a teaching regarding the maximum size allowable affects the minimum size that is taught." The answer is that the quoted passages demonstrate that Graham not only does not disclose structural gene elements with less than 30 nucleotides, but they are actively taught away from. There is no emphasis placed in Graham on a particular size class of molecules in the range currently being claimed and this is evidenced by Graham's teaching of an embodiment wherein

> [S]aid synthetic gene at least comprises multiple structural gene sequences wherein each of said structural gene sequences comprises a nucleotide sequence that is substantially identical to the nucleotide sequence of the target gene or a derivative thereof or a complementary sequence thereto and wherein the multiple structural gene sequences are placed operably under the control of a single promoter sequence. (Column 9, lines 55-64.)

and by Column 10's stipulation that the total length of the multiple structural gene sequence should be no more than, at a maximum, 500-2,000 bases. The relevant embodiment illustrated by Graham set forth in column 18 at lines 27-38, provides a construct with an inverted repeat or palindrome of a complete BEV polymerase open reading frame under the control of a single promoter. Thus, Appellants' point is not that the maximum size allowable affects the minimum size that is taught, but rather that Graham's focus is on constructs with structural genes much larger than 30 nucleotides.

Summary re Graham

In summary, Graham is silent on the length of RNA produced by Graham's constructs and Graham's disclosure falls short of any inherent teaching of the RNAs currently claimed. This is not only because the production of RNA molecules of 20-24 nucleotides in length is not even close to

an inevitable result of Graham's teachings, even if these could be interpreted as teaching structural gene elements that are 20-30 nucleotides in length, but also because Graham does not teach structural gene elements that can be as small as 20-30 nucleotides, and because Graham teaches a very large range of lengths of structural gene elements with emphasis on much larger members of the genus.

Fire and Graham

Claims 116-124 on appeal continue to be rejected under 35 USC 103(a) as being unpatentable over Fire (U.S. Patent No. 6,506,559) in view of Graham (U.S. Patent No. 6,753,099). At page 6, the EA states that Fire teaches a method of silencing which "comprises introducing into cells short RNA molecules." Respectfully, this is dead wrong. According to the support alleged in column 6, lines 32-43, silencing is accomplished by introducing double-stranded RNA – not "short" RNA molecules, and is acknowledged prior art. Column 7, at lines 30-31, simply says that "the RNA may comprise one or more strands of polymerized ribonucleotide." Column 7, line 53 to column 8, line 6, again says nothing about the length of the RNA molecules. The only size *ever* mentioned in the Fire specification is in column 8, at lines 5-6, that the "length of the *identical nucleotide sequences* may be at least 25, 50, 100, 200, 300 or 400 bases." Column 8, at lines 13-35, simply discusses organisms in which this occurs, and again is silent on the length of the RNA molecules.

The EA, at page 14, states that because Fire, at column 8, lines 5-6, states that "The length of the identical nucleotide sequences 'may be' at least 25, 50, 100, 200, 300, or 400 bases", this is permissive, and that, therefore, "other lengths for the nucleotide sequence are not excluded." This is not correct. When a parent says to a child: "You may play in the house or in the yard", this is not

permissive for the child to play in the street. To the extent that the language is permissive, it is permissive only for lengths of the sequence identity (not the whole molecule) equal to or greater than 25. Fire is permissive only of using lengths greater than 25, as the list itself skips from 25 to 50 and up from there.

The argument made in the bridging paragraph on pages 15-16 of the EA asserting that Fire teaches molecules of only 25 nucleotides in length is not correct, and it improperly characterizes what is asserted in the Appeal Brief. The Appeal Brief never argued, as stated at the top of page 15 of the EA, "that the RNA molecules taught by Fire have nucleotide sequences which are not part of the complementary, double stranded sequences, and discuss this in terms of the double stranded region being 25 nucleotides in length". Correctly stated, the Appellants' argument is as follows: The quotation from Fire in the Appeal Brief at page 10, referred to here for convenience as "**TEACHING A**" (Column 8, lines 5-6), only associates the numbers of nucleotides in the RNA used to induce silencing with the length of identical nucleotides to those in the target gene. It does not teach anything at all about the length of the duplex molecule itself. Fire, column 4, lines 20-23, cited by the Examiner, referred to here for convenience as "**TEACHING B**", provides that the RNA introduced into a cell may be fully double-stranded in character. Like **TEACHING A**, **TEACHING B** does not teach anything about the length of the molecules themselves. It might be correct to assert that if the molecule of Fire is fully double stranded in character (**TEACHING B**), at least 25 nucleotides of that duplex (**TEACHING A**) must be identical to nucleotides in the target gene, but this says nothing about the overall length of the fully double-stranded RNA molecule since, even if **TEACHING A** and **TEACHING B** are combined, this says nothing about the extent to which the fully double-stranded molecule contains additional sequences which have nothing to do

with the target gene. Thus, the conclusion drawn by the Examiner that Fire teaches molecules of 25 nucleotides is bogus and is not a logical result of the evidence cited.

In any case the present claims specifically require 20-24 nucleotides.

The EA also asserts the claims of Fire support short RNA, but they do not. Claim 10 dependent on claim 1, states that each of the nucleotide sequences "comprise" at least 25 bases that correspond to the target gene or are complementary thereto. This is completely consistent with the interpretation that the only mention of a number of nucleotides in the specification in column 8 refers only to the length of the identical nucleotide sequences in what is evidently envisioned as a larger molecule.

The other claim presumably referred to in the EA is claim 15, which depends from claim 12. Claim 15 states that "said double stranded ribonucleic acid structure is at least 25 bases in length and each of the ribonucleic acid strands is able to specifically hybridize to a DNA strand of the target gene over the at least 25 bases". There is no antecedent basis for "structure" in claim 12, so it is unclear what is being referred to. The "structure" is certainly consistent with the interpretation that this is simply a region of identity in view of the wording of the claim to require hybridizing over the same length. Both claim 1 and claim 12 refer to a double-stranded molecule, each strand "consisting essentially of" a sequence that is related to a target gene. This, too, is consistent with the description in column 8 of the identical sequence being a portion of the larger molecule since it is the sequence of identity that appears critical. The "consisting essentially of" language in claims 1 and 12 (former claim 22) was explicitly inserted only to exclude the presence of a hairpin loop in the constructs of a document by Agrawal, as stated in the response filed 8 January 2002.

With this explicit explanation for the amendment, it becomes clear that this limitation was not introduced to limit the length of the RNA molecules themselves.

The prosecution history of Fire was addressed in Appellants' Brief only as an aid to claim interpretation. Since the claims are referenced by the Examiner as indicating that Fire teaches RNA molecules that consist of only 25 nucleotides, Appellants demonstrate that an appropriate interpretation of the claims does not provide this teaching. Claims are read in light of the specification and prosecution history as required by *Phillips v. AWH Corp.*, 415 F3d 1303, 75 USPQ2d 1321 (Fed. Cir. *en banc* 2005). This also makes it relevant that size limitations were added to the claims only after the application was itself filed. It is not necessary to judge the validity of Fire's claims in order to conclude that the recitation of a nucleotide sequence that comprises at least 25 bases in claims 10 and 15 does not refer to the size of the RNA molecule itself, but rather, as stated in column 8, to the length of a sequence of identity with the target.

The issue is what the claims teach when properly interpreted and statements made in prosecution history, and especially the rationale for amendments to the claims, is a legitimate tool for claim construction. There is nothing in Fire that describes RNA molecules that contain only 25 nucleotides. There is no "consisting of" language that would limit the size of the molecules anywhere.

Even if the Examiner were correct that Fire "implies" that molecules as short as 25 nucleotides could be used, the EA properly concedes that there is no teaching in Fire of silencing genes using RNA molecules of only 20-24 nucleotides. Therefore, Graham is cited as putatively teaching that the RNA molecules of Fire could be even shorter than 25 nucleotides in length.

This is not correct. The Examiner has never pointed to any disclosure in Graham showing that Graham teaches or even suggests the production of any RNA of any specified length, or of 20-30 nucleotides as the EA suggests. Appellants will not repeat their arguments as to what Graham does or does not teach, as they have been set forth above. Suffice it to say that not only is Fire completely silent as to the length of the RNA molecules that might be used for gene silencing, so is Graham. Graham teaches the length only of DNA in a structural gene insert in a DNA construct, and nothing about the size of RNA that it produces. Graham doesn't even teach the size range of 20-30 nucleotides for the insert *per se* as was extensively argued above. The citation of *In re Aller*[*] is clearly inapposite since the general conditions of the claim are not disclosed in the prior art – neither Fire nor Graham suggests any length for RNA molecules that would be subject to optimization. Neither are the citations of *In re Wertheim* or *In re Woodruff*[†] appropriate, since the ranges assertedly described in Graham are not ranges disclosed by either Graham or Fire for RNA molecules *per se*.

In response to Appellants' argument that even the 25 nucleotide required minimum refers not to the length of the RNA molecules *per se*, but rather to the sequences of identity to the target gene, the EA at page 15 argues that RNA molecules of this length are not specifically excluded and that Appellants' position is that the RNA molecules of Fire must contain additional sequence beside the sequence of identity. This misstates the issue. The issue is whether Fire discloses or suggests

[*] *Aller* concerned optimizing temperature and reagent concentrations in a known process for making acetone, not a discovery of the nature of a molecule involved in a complex process.

[†] The problem in *Wertheim* was that the criticality of the claimed range for various parameters in making instant coffee was never disclosed in the specification; the problem in *Woodruff* is that the unexpectedly good results were obtained by modifying the range in the claims. In the present case, the invention specifically lies in the criticality of the size of the RNA. The ability to use short RNA molecules rather than the long strands taught by Fire makes the use of RNA in gene silencing more practical.

RNA molecules that consist of this length or shorter, and Fire does not. Fire only discloses RNA molecules with sequences of identity with 25 or many more nucleotides.

The remaining argument in Appellants' Brief regarding interferon was introduced simply to aid in the interpretation of what Graham and Fire do or do not disclose. The assertion by the Examiner that "It is also noted that the instant specification makes no mention whatsoever of the interferon response" is irrelevant. Appellants do not need "to rely on the avoidance of the interferon response as an unexpected result to overcome the rejection", as their disclosure specifically teaches the use of short RNA molecules to induce silencing and it was already known that molecules in this size class do not invoke the interferon response. In Graham and Fire, the failure to mention this response is evidence that, in spite of their putative knowledge of the interferon response, they did not note that small RNAs, if part of their disclosures, would have this advantage, or suggest that such small RNAs were included in their work.

The disclosure of Graham regarding problems with working with long synthetic palindromes (Graham, col. 10, lines 26-32), relates to multiple, rather than long palindromes. Graham is discussing the number of structural genes to be employed in a single construct.

In response to the arguments in the Brief that Graham and Fire concern different mechanisms altogether, the Examiner simply states that the embodiments of Graham produce sense and antisense RNAs similar to the RNAs in Fire. However, in fact, there is no teaching in Graham that they do so. There is no response to the arguments made in the Brief that RNA administered directly to the cell, as required by the claims subject to this rejection, does not have to contain features that would have to be included in constructs designed to generate RNA intracellularly, so

the number of nucleotides in any structural gene does not bear a 1:1 relationship to the number of nucleotides in directly administered RNA.

In summary, Fire does not teach RNA molecules in any particular nucleotide size range, nor does Graham. Even Fire's teaching of sequences of identity of at least 25 nucleotides as an absolute minimum is outside the range of the claimed RNA. Graham cannot remedy this, both because Graham itself teaches nothing about the size of RNA molecules and because Graham requires a minimum of 30 nucleotides even in Graham's structural gene inserts.

Brown

Claims 116-130 continue to be rejected under 35 USC 103(a) as being unpatentable over Brown, *et al.* (U.S. Patent No. 6,723,987). After reciting the claim limitations on page 9 of the EA, the Examiner states that "None of the appealed claims require the SARMs and SSRMs to be complementary to each other." Why this would be relevant is unclear to Appellants.

Brown is not concerned with disclosing new ways to silence genes; Brown simply refers to prior art. Brown wants simply to silence genes in the gibberellin synthesis pathways. Among the prior art approaches cited as set forth in column 3 are antisense methods, ribosomes, triplex DNA, cosuppression or "any other well known methods for reducing the expression of endogenous plant genes." The Examiner focuses on two of these "cosuppression" and "antisense" and suggests that by performing these at the same time, the invention would result, provided the sequences used for cosuppression and antisense were of the proper length. The Examiner appears to assume that "cosuppression" involves the use only of a sense sequence which is not entirely clear since cosuppression involves introducing a DNA encoding a particular gene which may itself be double-stranded and sometimes results in the silencing of an endogenous gene (see Jorgensen 1990 and

many other references of record. See also the present application, page 23, line 15 – page 24, line 2.)

Assuming that the "combination of cosuppression and antisense" really refers to supplying a sense and antisense strand (both of RNA? both of DNA? one of which is RNA and the other DNA?), the suggestion to combine such strategies is nowhere found in Brown. To assume that combining such strategies would lead to a better result has no basis in the art or in Brown itself.

This proposition is equivalent to proposing that if the goal of an action is to raise a piano to the second story of a building, one should both raise the piano by a hoist and carry the piano up the stairs, since because each strategy on its own might be successful, using both is even more likely to be successful.

Cosuppression and antisense approaches are vastly different strategies utilizing different starting materials. It is not even likely that combining these strategies makes any sense.

Thus, Brown does not come close to suggesting using a combination of sense RNA molecules and antisense RNA molecules or constructs generating them to effect silencing, much less suggesting any particular size.

As for the size of the nucleic acid constructs that Brown suggests for mechanisms involving various methods of silencing (which apparently can include any art-known method) Appellants find nothing that would encourage the reader to focus on 20-24 nucleotides.[‡]

The EA states, at page 23, that it "would have been obvious to make the sequences of any size taught by Brown, including 20-24, to determine optimal workable conditions". Taking this argument literally, and considering the range of sizes listed (for antisense only) in column 3,

[‡] The argument on page 22 of the EA, that Brown does not require use of a polyadenylation signal or transcription termination signals, seems completely irrelevant.

lines 60-67, it would, therefore, be obvious to the ordinarily skilled artisan to focus on making molecules of 10-15 nucleotides (which are not operative at all), or 1,000-10,000 which might be operative, but cumbersome to make, and this is precisely the point. Without any reason to focus on the particular size class of 20-24, claimed by the Appellants, it would not have been obvious to focus on production of that size class. Given the size of the range disclosed by Brown, even assuming Brown relates somehow to using sense and antisense RNAs for silencing, optimization would not have been a matter of routine experimentation. Therefore citations of *In re Aller*, *In re Wertheim*, and *In re Woodruff*, are inapposite. The further discussion of sizes in column 5, at lines 50-55 of Brown, are equally broad in range, and not even tied to any particular type of nucleic acid molecule (RNA or DNA) or any means of silencing. If one were looking to Brown for guidance as to the size of even antisense or miscellaneous methods of expression, Brown's guidance would clearly not lead one to the very specific 20-24 nucleotide range claimed.

Appellants point out once again that it is the finding of this size range as significant that is the invention. Appellants have acknowledged the work of Fire and Mello showing that double-stranded RNA is able to silence gene expression. Appellants' contribution is to determine that the mechanism involves specifically short RNA molecules. All of the claims are directed to methods to silence genes using these short sequences.

It is really difficult to understand how Brown can be understood to suggest the invention as claimed. Brown is concerned with shutting down gibberellin synthesis pathways by whatever means are available in the art. Brown teaches nothing about silencing genes using a combination of sense and antisense strands of RNA of any size, much less the specific sizes required by the claims.

Appellants' comments on "secondary considerations"

Appellants appreciate the acknowledgement by the Examiner at pages 23-24 of the EA that the present inventors have been recognized as making a significant contribution to the art. The citation of the prizes won by Dr. Baulcombe are not characterized by Appellants as secondary considerations, but rather as guides to what is actually taught in the art. In order to come to the conclusion that Graham anticipates the present claims, the Examiner is interpreting the disclosure of Graham as actually teaching what the present Appellants have invented. If that were what Graham taught, then Graham should have obtained these prizes. Similarly, if the combination of Graham and Fire suggested what Appellants have claimed, then Appellants should not have been entitled to these prizes – hence Appellants' position that the combination of Graham and Fire do not suggest what they have claimed. As to Brown, similarly, if Brown suggested the present claims, the contribution made by the inventors would not have been characterized as the advance that has been recognized. These are not secondary considerations, but rather guides to what Graham, Fire and Brown do or do not teach.

Conclusion

Because of the work of the Appellants, it is now understood that the mechanism of post-transcriptional gene silencing specifically involves short RNA molecules of 20-24 nucleotides both short sense RNA molecules and short antisense molecules being present. Prior to Appellants' invention, there was no understanding in the art that this was the case. The cited portions of Graham, Fire and Brown all represent disclosures of wide ranges of sizes that are putatively operable even if these sizes were interpreted to refer to the size of sense and antisense RNA molecules that induce silencing.

There is no way to read Graham, Brown, or Fire plus Graham to teach or suggest what the Examiner states to be their teachings and suggestions without reading the teachings of the present invention into them. This is clearly improper.

Appellants respectfully request that the rejections be withdrawn and claims 116-130 be passed to issue on an expedited basis.

An Oral Hearing is requested.

The Assistant Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.17 that may be required by this Reply Brief, or to credit any overpayment, to **Account No. 03-1952**.

Respectfully submitted,

Dated: August 26, 2009 By: / Kate H. Murashige /

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CLAIMS APPENDIX

1-115. (canceled)

116. (previously presented): A method of silencing a gene in cells by post-transcriptional gene silencing (PTGS) which method comprises introducing into said cells a composition that contains short RNA molecules (SRMs),

which SRMs are isolated short sense RNA molecules (SSRMs) and isolated short antisense RNA molecules (SARMs) at the same abundance;

wherein said SARMs are complementary to a region of a target RNA transcribed from a gene which is silenced when said short RNA molecules are present in cells containing said gene and said SSRMs correspond to said target RNA; and

wherein the SSRMs and SARMs consist of 20, 21, 22, 23 or 24 nucleotides,

whereby said gene is silenced.

117. (previously presented): The method of claim 116, wherein the cells are contained in an organism and said introducing comprises administering said SRMs to the organism.

118. (previously presented): The method of claim 116, wherein the SRMs are synthetic.

119. (previously presented): The method of claim 116, wherein the SARMs have a structure complementary to a target mRNA transcribed from a gene endogenous to a plant, a mammal, an avian organism, a reptile, an insect, a protozoan, a nematode, or a virus.

120. (previously presented): A method of silencing a gene in cells of an organism by post-transcriptional gene silencing (PTGS) which method comprises introducing into said cells a composition that contains isolated short antisense RNA molecules (SARMs) and isolated short sense RNA molecules (SSRMs) corresponding to a target RNA transcribed from said gene, the nucleotide sequences of which consist of 20, 21, 22, 23 or 24 nucleotides and wherein said SARMs can base pair with said target RNA.

121. (previously presented): The method of claim 120, wherein said SARMs and SSRMs are present at the same abundance.

122. (previously presented): The method of claim 120, wherein the cells are contained in an organism and said introducing comprises administering said SSRMs and SARMs to the organism.

123. (previously presented): The method of claim 120, wherein the SSRMs and SARMs are synthetic.

124. (previously presented): The method of claim 120, wherein the SARMs have a sequence that can base pair to a target mRNA transcribed from a gene endogenous to a plant, a mammal, an avian organism, a reptile, an insect, a protozoan, and a nematode, or a virus.

125. (previously presented): A method of silencing a gene in cells by post-transcriptional gene silencing (PTGS) which method comprises introducing into said cells a composition that contains at least one vector that, when introduced into said cells, produces short RNA molecules (SRMs),

which SRMs are short sense RNA molecules (SSRMs) and short antisense RNA molecules (SARMs);

wherein said SARMs are complementary to a region of a target RNA transcribed from a gene which is silenced when said short RNA molecules are present in cells containing said gene and said SSRMs correspond to said target RNA; and

wherein the SSRMs and SARMs consist of 20, 21, 22, 23 or 24 nucleotides,

whereby said gene is silenced.

126. (previously presented): The method of claim 125, wherein the cells are contained in an organism and said introducing comprises administering said composition to the organism.

127. (previously presented): The method of claim 125, wherein the SARMs have a structure complementary to a target mRNA transcribed from a gene endogenous to a plant, a mammal, an avian organism, a reptile, an insect, a protozoan, a nematode, or a virus.

128. (previously presented): A method of silencing a gene in cells of an organism by post-transcriptional gene silencing (PTGS) which method comprises introducing into said cells a composition that contains at least one vector that, when introduced into said cells, produces short antisense RNA molecules (SARMs) and short sense RNA molecules (SSRMs) corresponding to a target RNA transcribed from said gene, the nucleotide sequences of which consist of 20, 21, 22, 23 or 24 nucleotides and wherein said SARMs can base pair with said target RNA.

129. (previously presented): The method of claim 128, wherein the cells are contained in an organism and said introducing comprises administering said composition to the organism.

130. (previously presented): The method of claim 128, wherein the SARMs have a sequence that can base pair to a target mRNA transcribed from a gene endogenous to a plant, a mammal, an avian organism, a reptile, an insect, a protozoan, a nematode, or a virus.